REMARKS

The invention, as currently claimed, features fusion proteins.

Amendments

Applicants have amended claim 1 to specify that the claimed fusion protein includes a first domain to which a ligand binds that includes a steroid hormone receptor and a second domain that (i) comprises a steroid hormone receptor and (ii) associates when a ligand binds to the first domain. Support for these claim amendments can be found in the specification, for example, at page 4 (lines 23-24) and page 6 (lines 4-21). Claim 3 has been amended to specify that the steroid hormone receptor is an estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor, or mineral corticoid receptor. Support for this claim amendment can be found, for example, at page 6 (lines 4-7). Applicants have also amended claim 4 to depend from claim 2. Finally, applicants have added new dependent claims 18-24. Support for these new claims is found, for example, in Figure 1 and the accompanying passages of the specification referring to this figure.

Office Action

Claims 1-4 are pending in the application. Claims 1-4 were rejected under 35 U.S.C. § 112, first paragraph. This rejection is addressed as follows.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-4 were rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure in applicants' specification (1) fails to provide a written description of the claimed invention and (2) does not enable the claimed fusion proteins. For the following reasons, each of these rejections is respectfully traversed.

Written Description

Claims 1-4 were rejected, under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention. The Examiner states: "[t]he fusion proteins have been defined in terms of how the various components are to function, not in terms of what they are." Applicants respectfully traverse this basis of the rejection as applied to the amended claims.

The adequate written description requirement of 35 U.S.C. § 112, ¶ 1 provides that

> the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...

The written description requirement serves "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material." *In re Wertheim*, 541 F.2d 257, 262, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976). In order to meet the written description requirement,

the applicant need not utilize any particular form of disclosure to describe the subject matter claimed, but "the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989) (citation omitted). Stated another way, "the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

Moreover, the burden is on the Examiner to challenge the adequacy of applicants' written description of the invention. As stated by the MPEP (§ 2163.04):

> The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97. (emphasis added)

The claims in question are generally directed to products that include the inventors' novel fusion proteins. Independent claim 1, as amended, for example, reads:

1. A fusion protein comprising (a) a first domain to which a ligand binds that comprises a steroid hormone receptor, (b) a second domain that (i) comprises a steroid hormone receptor and (ii) associates when a ligand binds to the first domain, and (c) a third domain comprising a cytokine receptor or a part thereof that imparts proliferation activity to a cell upon the association of the second domain.

As an initial matter, applicants note that the Examiner has failed to provide any specific reasoning as to why the present specification is inadequate. Rather, the Examiner summarily dismisses the description as insufficient and has erroneously placed the burden on Applicants to prove otherwise. On this basis alone, the rejection is fundamentally flawed and should therefore be withdrawn. Applicants have, however, addressed the substance of the Examiner's assertion with the present claim amendments.

Applicants further note that their specification describes to the skilled worker what is now claimed. See, for example, page 4 (lines 3-7); page 4 (lines 15-16); page 4 (lines 23-24); and page 6 (lines 4-21). And Figure 1 depicts several examples of fusion proteins. Furthermore, the respective domains are described by "what they are." Clearly, based on this description, one skilled in the art would readily recognize that applicants invented the claimed fusion proteins, and, on this basis alone, the rejection may be withdrawn.

In sum, there can be no question that applicants were in possession of the claimed genus at the time their application was filed, and that one skilled in the art would recognize applicants' disclosure as a description of the invention defined by the present claims. As a

result, applicants' specification clearly satisfies the written description requirement, as set forth by the case law, and applicants request reconsideration and withdrawal of this basis for the § 112 rejection.

Enablement

Claims 1-4 also were rejected under § 112, first paragraph, on the basis that the specification fails to enable the skilled artisan to make and use the invention. This rejection should be withdrawn.

The current Office Action contends that the specification does not provide guidance on "just what the starting materials are or the reaction conditions under which the resultant product can be used." To support this contention, the Office relies largely on *Genentech v. Novo Nordisk A/S*, but this reliance is largely misplaced because the facts presented in this case do not parallel those presented in *Genentech*. In *Genentech*, the court found that there was no disclosure of any specific starting material to be used for making cleavable human growth hormone ("hGH") fusion proteins.[1] In contrast to *Genentech,* where the specification failed to disclose a useful conjugate hGH protein or method for its cleavage, applicants'

[1] One of the questions before the court was whether the specification would have enabled a person having ordinary skill in the art at the time of filing to use cleavable fusion expression to make hGH without undue experimentation. The accompanying specification did not describe *in any detail whatsoever* how to make hGH using cleavable fusion expression. For example, no reaction conditions for the steps needed to produce hGH were provided; no description of any specific cleavable conjugate protein appeared. The relevant portion of the specification merely described three (or perhaps four) applications for which cleavable fusion expression is generally well-suited and then names an enzyme that *might be* used as a cleavage agent (trypsin), along with sites at which it cleaves ("arg-arg or lys-lys, etc."). Thus, the specification did not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work. Moreover, neither the specification nor any of the supporting references suggested a single amino acid sequence, out of the virtually infinite range of possibilities, that would yield hGH in a useful form when cleaved from the conjugate protein. The court found this lack of enabling detail to be fatal.

specification not only provides ample description of the methods for making and using the claimed fusion proteins, but in fact demonstrates actual reduction to practice several times. For example, the Examiner's attention is directed to Examples 1 and 4, working examples which describe the construction of three selective amplification fusion genes of the present invention - GCRER, GCRΔ(5-195)/ER, GCRΔ(5-195, 725-726)/ER, alone and ligated with IRES-CD24. The remaining examples describe, in detail sufficient detail to enable one of ordinary skill in the art to replicate same, the introduction of the fusion genes into cells (see, e.g., Example 2) and the use of such fusion genes to enable selective amplification of transformed cells (see, e.g., Examples 3 and 5). Applicants submit that these examples are sufficiently detailed to allow one of ordinary skill in the art to reproduce the invention.

Applicants also point out that, to sustain an enablement rejection, the Office has the initial burden to establish a reasonable basis to question the enabling nature of an applicants' specification. Thus, in a case in which the PTO questions the enablement of a claim, the CCPA, in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367, 369 (CCPA 1971) has stated that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (emphasis added).

The MPEP (§ 2164.04) further emphasizes the *Marzocchi* standard in stating that:

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy

> of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (emphasis added).

Here, applicants note that no scientific evidence currently made of record in this case establishes a basis for doubting the objective truth of the statements found in applicants' specification regarding enablement with respect to making the claimed fusion proteins falling within the scope of applicants' claims. Moreover, the Examiner has provided no evidence or reason for doubting applicants' teaching on making the claimed fusion proteins. On this basis alone the facts in the present case compel withdrawal of the § 112, first paragraph enablement rejection, and applicants request reconsideration on this issue.

Applicants also submit that the processes of plasmid construction and cellular transformation have become routine in the art[2] such that overwhelming detail of starting materials and reaction conditions is not required. Furthermore, it is well accepted that an

[2] As evidence of this assertion applicants direct the Examiner's attention to the Materials and Methods sections of the five references accompanying this communication: Burk et al., EMBO J. 10:3713-3719, 1991; Superti-Furga et al., Proc. Natl. Acad. Sci. USA 88:5114-5118, 1991; Boehmelt et al., EMBO J. 11: 4641-4652, 1992; Jackson et al., EMBO J. 12: 2809-2819, 1993; and Ito et al., Blood 90: 3884-3892, 1997. The post-filing priority date Ito reference was co-authored by several of the instant inventors.

applicant preferably omits from a patent specification description that which is well known in the art.[3] Moreover, with respect to the labels "fragment 1" and the like, since the sequences and/or structure of the plasmids were known or readily determined and the sequences cleaved by the enumerated restriction enzymes (e.g., HindIII and EcoRI) were known, it is not necessary to provide explicit sequence and/or structure description of the resulting fragments to enable their production and use.

Accordingly, applicants respectfully submit that the skilled artisan would have absolutely no difficulty in making or using the claimed fusion proteins. This rejection may now be withdrawn.

Information Disclosure Statement

Applicants also direct the Examiner to Information Disclosure Statement submitted in connection with this application on September 19, 2002. Applicants request that the Form PTO-1449 accompanying this Statement be initialed and returned with the next action.

[3] The case law is clear clear "a patent need not teach, and preferably omits, what is well known in the art."*See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir. 1988); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 954 (1987) ("A patent need not teach, and preferably omits, what is well known in the art."); *see also Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 804 F.2d 659, 231 USPQ 649 (Fed. Cir. 1986) ("A patent applicant need not include in the specification that which is already known to and available to the public.").

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

Applicants note that the Office action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

Paul T. Clark
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110

Enclosed is a Petition for Extension of Time and a check in the amount of $460.00 for the required fee. Also enclosed is a check in the amount of $36.00 for the newly added dependent claims.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: November 7, 2002

James D. DeCamp, Ph.D.
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Version of Specification and Claims Showing Changes Made

In the Title:

Amend the title from

"GENE THAT IMPARTS SELECTIVE PROLIFERATION ACTIVITY" to

--FUSION PROTEIN THAT IMPARTS SELECTIVE PROLIFERATION ACTIVITY --.

In the Claims:

Amend claims 1-4 as follows.

1. (Amended) A fusion protein comprising (a) a first [ligand-binding] domain to which a ligand binds that comprises a steroid hormone receptor, (b) a second domain that (i) comprises a steroid hormone receptor and (ii) associates when a ligand binds to the first domain [of (a)], and (c) a third domain comprising a cytokine receptor or a part thereof that imparts proliferation activity to a cell upon the association of the second domain.

2. (Amended) The fusion protein of claim 1, wherein the third domain ["domain comprising a cytokine receptor or a part thereof that imparts proliferation activity to a cell upon the association"] is derived from a G-CSF receptor.

3. (Amended) The fusion protein of claim 1, wherein the [first "ligand-binding" domain is derived from a] steroid hormone receptor is an estrogen receptor,

androgen receptor, progesterone receptor, glucocorticoid receptor, or mineral corticoid receptor.

4. (Amended) The fusion protein of claim [3] 2, wherein the steroid hormone receptor is an estrogen receptor.

Please add the following new claims 18-24.

18. (New) The fusion protein of claim 4, wherein the third domain comprises the entire G-CSF receptor.

19. (New) The fusion protein of claim 4, wherein the third domain comprises a mutant G-CSF receptor that lacks reactivity against G-CSF.

20. (New) The fusion protein of claim 19, wherein the mutant G-CSF receptor lacks the extracellular domain of wild-type G-CSF.

21. (New) The fusion protein of claim 19, wherein the mutant G-CSF receptor is deficient in amino acid residue 5 (Glu) through 195 (Leu) of wild-type G-CSF.

22. (New) The fusion protein of claim 4, wherein the third domain comprises a mutant G-CSF receptor that lacks reactivity against G-CSF and the ability to induce differentiation.

23. (New) The fusion protein of claim 22, wherein the mutant G-CSF receptor lacks both the extracellular domain and the differentiation-inducing domain of wild-type G-CSF.

24. (New) The fusion protein of claim 23, wherein the mutant G-CSF receptor is deficient in amino acid residues 5 (Glu) through 195(Leu) as well as amino acid residues 725 through 756 of wild-type G-CSF.